Preclinical activity for TPX-4589 (LM-302), an antibody-drug conjugate targeting tight junction protein CLDN18.2 in solid tumors

Poster #116

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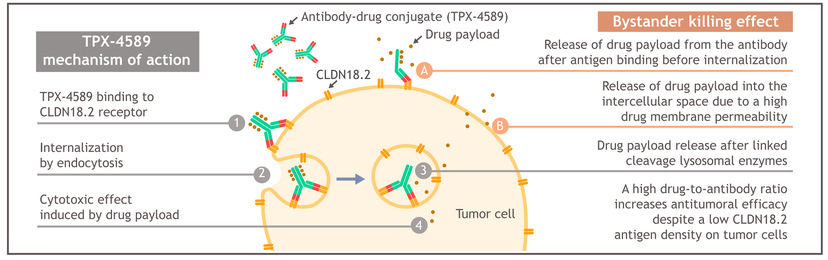
Introduction

- Isoform 2 of claudin 18 (CLDN18.2) is a tight junction protein involved in the regulation of epithelial cell permeability, barrier function, and polarity[1]
  - In healthy tissue, CLDN18.2 is selectively expressed in tight junctions of gastric epithelial tissue, largely inaccessible to intravenous antibodies[1-3]
  - On malignant transformation, CLDN18.2 is exposed on the cancer cell surface and expressed in many solid tumors, including gastric tumors and pancreatic tumors[1,2]
  - CLDN18.2 expression is associated with tumor pathogenesis, proliferation, and metastasis, making it a promising target for cancer therapies[1,4]
- TPX-4589, a novel antibody-drug conjugate (ADC) developed to target CLDN18.2, is comprised of a recombinant humanized anti-CLDN18.2 IgG1 monoclonal antibody (mAb) [LM-102] coupled with cytotoxic payload monomethyl auristatin E (MMAE) (**Figure 1**)
- Here we present preclinical studies conducted to characterize TPX-4589 in CLDN18.2-positive cells, including binding affinity, internalization, ADCC, cell proliferation inhibition, and in vivo efficacy in gastric and pancreatic tumor models

Figure 1: TPX-4589 Mechanism of Action



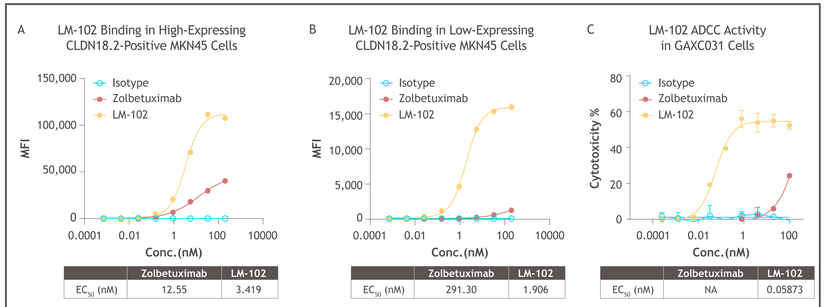
Materials and Methods

- In vivo analyses were performed in MKN45, GAXC031, MIA PaCa2, PAX031, and PAX040 cell lines
- High or low CLDN18.2 expression was defined by:
  - Flow cytometry (FACS) ratio (top median fluorescence intensity [MFI] of LM-102/top MFI of isotype) in MKN45, GAXC031, and MIA PaCa2 cell lines
    - Ratios >100 fold and <100 fold were defined as high or low CLDN18.2 expression, respectively, in MKN45 cells
    - Ratio >1000 fold in high endogenous CLDN18.2-expressing GAXC031 cells
    - Ratio ~500 fold in high endogenous CLDN18.2-expressing MIA PaCa2 cells
  - Immunohistochemistry (IHC) staining in PAX040 and PAX031 cell lines

TPX-4589 Component Antibody LM-102 Binding Affinity and ADCC Activity

- LM-102, the anti-CLDN18.2 mAb component of TPX-4589, showed improved binding affinity in both high- (Figure 2A) and low-expressing (Figure 2B) CLDN18.2-positive cells compared with zolbetuximab, an investigational mAb that specifically binds CLDN18.2
- LM-102 showed concentration-dependent ADCC activity superior to zolbetuximab (**Figure 2C**)

Figure 2: LM-102 Binding to High- and Low-Expressing CLDN18.2-Positive Cells and ADCC Activity



	Zolbetuximab	LM-102
EC_{50} (nM)	12.55	3.419

	Zolbetuximab	LM-102
EC_{50} (nM)	291.30	1.906

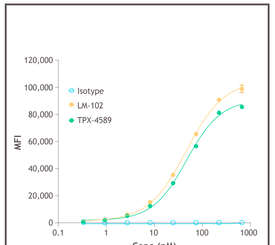
	Zolbetuximab	LM-102
EC_{50} (nM)	NA	0.05873

ADCC, antibody-dependent cellular toxicity; mAb, monoclonal antibody; MFI, median fluorescence intensity.

TPX-4589 Binding and Internalization

- TPX-4589 bound to endogenous CLDN18.2-expressing GAXC031 gastric cancer cells in a dose-dependent manner, with an EC_{50} of 47.25 nM
- TPX-4589 binding affinity was similar to LM-102 (EC_{50} 46.44 nM) (**Figure 3**)
- TPX-4589 internalization was shown in both high- (Figure 4A) and low-expressing (Figure 4B) CLDN18.2-positive cells
- TPX-4589 internalization was similar to that shown for LM-102 and was superior when compared with zolbetuximab (**Figure 4C**)

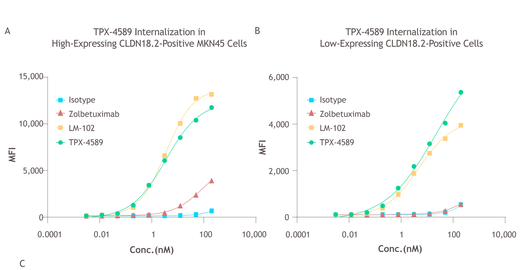
Figure 3: TPX-4589 Binding Affinity to GAXC031 Gastric Cancer Cells



	TPX-4589	LM-102
EC_{50} (nM)	47.25	46.44

MFI, median fluorescence intensity.

Figure 4: TPX-4589 Internalization in Both High- and Low-Expressing CLDN18.2-Positive MKN45 Cells



C

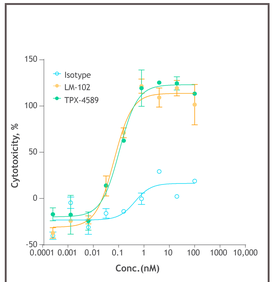
	MKN45 cell line	TPX-4589	LM-102	Zolbetuximab	Control hIgG1
EC_{50} (nM)	High CLDN18.2 expression	3.5	3.5	83.93	NA
	Low CLDN18.2 expression	22.4	4.8	NA	NA

MFI, median fluorescence intensity.

TPX-4589 In Vitro Activity

- TPX-4589 showed concentration-dependent ADCC comparable to LM-102 (**Figure 5**)
- TPX-4589 inhibited in vitro tumor cell proliferation with nanomolar potency in GAXC031 (**Figure 6A**) and MIA PaCa2-high (**Figure 6B**) CLDN18.2-expressing cell lines, with superior growth inhibition versus LM-102

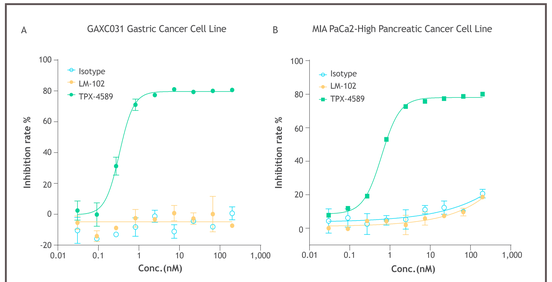
Figure 5: TPX-4589 ADCC



	TPX-4589	LM-102
EC_{50} (nM)	0.1076	0.06607

ADCC, antibody dependent cellular toxicity.

Figure 6: TPX-4589 Tumor Cell Proliferation Inhibition in CLDN18.2-Expressing Gastric and Pancreatic Cancer Cell Lines



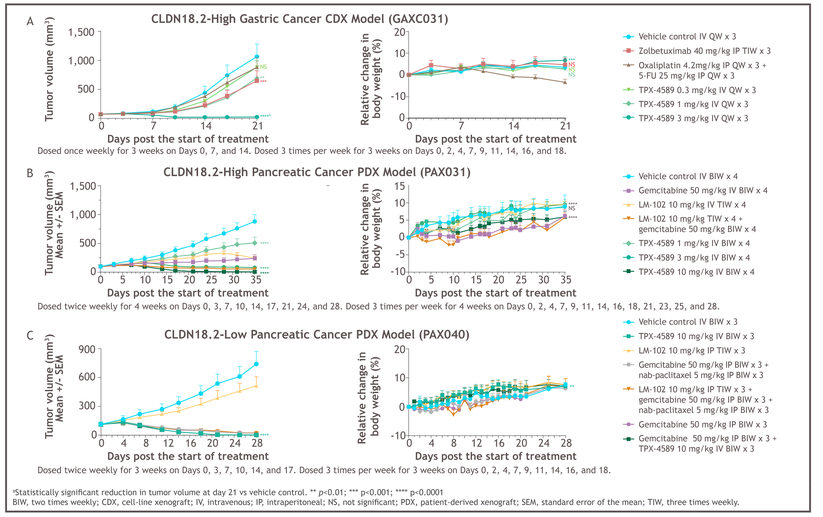
	TPX-4589
EC_{50} (nM)	0.3321

	TPX-4589
EC_{50} (nM)	0.6210

TPX-4589 In Vivo Efficacy

- In a CDX gastric cancer tumor model with high CLDN18.2 expression (GAXC031), TPX-4589 significantly reduced tumor volume in a dose-dependent manner and demonstrated superior efficacy to zolbetuximab and oxaliplatin + 5-FU (**Figure 7A**)
- In a CLDN18.2-high PDX pancreatic cancer tumor model (PAX031), increasing doses of TPX-4589 demonstrated superior tumor growth inhibition compared with single-agent gemcitabine and LM-102 and superior efficacy to LM-102 + gemcitabine at the highest dose tested (**Figure 7B**)
- In a PDX pancreatic cancer tumor model with low CLDN18.2 expression (PAX040), TPX-4589 alone demonstrated potent tumor growth inhibition (**Figure 7C**)

Figure 7: TPX-4589 Tumor Growth Inhibition in CLDN18.2-Expressing Gastric and Pancreatic Cancer Xenograft Tumor Models



[a]Statistically significant reduction in tumor volume at day 21 vs vehicle control. ** p<0.01; *** p<0.001; **** p<0.0001
BIW, two times weekly; CDX, cell-line xenograft; IV, intravenous; IP, intraperitoneal; NS, not significant; PDX, patient-derived xenograft; SEM, standard error of the mean; TIW, three times weekly.

Conclusions

- TPX-4589 is a novel CLDN18.2-targeting ADC that targets CLDN18.2, a tight junction protein expressed on the cell surface of many solid tumors, including gastric and pancreatic cancers
- TPX-4589 potently inhibited tumor cell proliferation in vitro and reduced tumor growth in vivo in both high and low-expressing gastric and pancreatic CDLN18.2 tumor models
- TPX-4589 showed superior internalization and efficacy compared with zolbetuximab in a gastric cancer tumor model
- These data suggest that TPX-4589 is a promising therapeutic candidate that warrants further investigation in clinical studies
- A phase 1/2 dose escalation and expansion study (NCT05001516) of TPX-4589 in patients with CLDN18.2-positive advanced solid tumors is currently ongoing

References

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